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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

IMMUNEX CORPORATION; AMGEN MANUFACTURING, LIMITED; and HOFFMANN-LA ROCHE INC.; Plaintiffs, v. SANDOZ INC.; SANDOZ INTERNATIONAL GMBH; and SANDOZ GMBH; Defendants.	Civil Action No.: 2:16-cv-01118-CCC-MF **Opening claim construction brief by Immunex Corporation and Amgen Manufacturing, Limited** Submitted herewith: 1. Declaration of Dr. Randolph Wall; 2. Declaration of Dr. Johann Gudjonsson; 3. Declaration of Vernon M. Winters (authenticating documents) 4. Declaration of James A. High Jr. (providing updated JCCS)

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Table of Abbreviations

For the Court's ease of reference, this brief uses the following abbreviations. Other abbreviations are defined in the brief.

Abbreviation	Full phrase
FDA	United States Food and Drug Administration
GD	Declaration of Dr. Johann Gudjonsson
JHD	Declaration of James A. High, Jr. Attaching Updated Joint Claim Construction Statement for Ease of Reference
Patent Office	United States Patent and Trademark Office
PTAB	Patent Trial and Appeal Board of the United States Patent and Trademark Office
RWD	Declaration of Professor Randolph Wall, Ph.D.
'182 Patent	US Patent No. 8,063,182
'522 Patent	US Patent No. 8,163,522
'225 Patent	US Patent No. 7,915,225
'605 Patent	US Patent No. 8,119,605
'631 Patent	US Patent No. 8,722,631; citations herein to the patents listed in this table will follow this form: '182 Patent X:Y-Z, with X as the column number, Y as the starting line number, and Z as the ending line number.
VWD	Declaration of Vernon M. Winters in Support of Opening Claim Construction Brief by Immunex Corporation and Amgen Manufacturing Ltd.
JCCS	Joint Claim Construction and Prehearing Statement (Dkt. No. 119)

I. Introduction

This case centers on a highly successful biological product called Enbrel® that is used to treat patients with rheumatoid arthritis, psoriasis, psoriatic arthritis, and other inflammatory conditions. Enbrel brings life-changing relief to patients, and as a result, is one of the most successful pharmaceutical products on the market today. Defendants seek to profit from Enbrel's success by marketing their "biosimilar" copy of Enbrel.

In auto-immune diseases like those noted above, the body's immune system attacks its own tissues, triggering inflammation, which causes pain, swelling, and injury. One substance that participates in this inflammatory response is called tumor necrosis factor or "TNF." Enbrel is an engineered molecule designed to bind TNF and prevent it from causing further inflammation. Enbrel's structure has two parts—a fragment of a human TNF receptor and a fragment of an antibody—that are fused together to form a novel, non-naturally occurring "fusion" protein.

As revealed in Patent Office proceedings, this "fusion" protein was contrary to conventional wisdom at the time of the patent filings, and the molecule exhibits surprising and unexpected properties. While the TNF receptor fragment of Enbrel specifically binds to TNF, that portion, if given alone, would not stay in circulation long enough to have any impact on reducing inflammation. Enbrel's antibody portion functions in its natural setting to promote inflammation. The concept of

combining them in one molecule for use in treating inflammatory conditions was a breakthrough. Based on its clinical success, Enbrel clearly met a long-felt need for patients suffering from TNF-mediated diseases.

Roche owns the patent granted on this novel fusion protein ("the '182 Patent"), as well as the patent that claims the DNA and methods to make it ("the '522 Patent") (collectively the "Roche Patents"). Immunex Corporation owns the FDA application on Enbrel, and also owns patents on novel methods for using the protein to treat certain diseases ("the '225, '605, and '631 Patents") (the "Immunex Patents"). Roche licensed the Roche Patents to Immunex, which sublicensed them to Amgen Manufacturing, Ltd. (referred to, with Immunex, as "Immunex").

Sandoz's biosimilar is an Enbrel copy. Like Enbrel, it combines the same two fragments into a new protein. Sandoz's copy has the same primary amino acid sequence, the same protein structure, and is proposed to treat the same diseases as Enbrel. And, like Enbrel, Sandoz's copy is able to stably and strongly bind TNF.

The claim construction issues presented in this case are straightforward. As set out below, all the contested terms should be construed to have their plain and ordinary meaning to one of skill in the art at the time of the respective filings. That is how the terms are used in the specifications and how the claims were understood during the Patent Office's examination. Sandoz dissembles the plain meaning in a litigation-driven attempt to manufacture non-infringement and invalidity issues.

But neither the intrinsic nor extrinsic evidence supports Sandoz's constructions.

Immunex's claim construction positions are fully supported by the intrinsic record of the patents and their prosecution histories and capture the plain meaning of the claim terms as would be understood by a person of skill in the art. Sandoz's are not and should be rejected.

II. Claim Construction Principles

Claim construction's purpose is to define the proper scope of patented invention. As the Supreme Court held in *Teva Pharm. USA v. Sandoz, Inc.*, 135 S.Ct. 831, 838 (2015), claim construction is an issue of law for the court to decide that may involve underlying issues of fact as to the meaning of terms to a person of skill in that technical field. The Federal Circuit's opinion in *Phillips v. AWH Corp*., 415 F.3d 1303 (Fed. Cir. 2005) (*en banc*), instructs that claims are construed through the eyes of the hypothetical person of ordinary skill in the relevant art at the time of the invention ("Ordinary Artisan"). *Phillips*, 415 F.3d at 1313. Through that lens, the claims have their plain and ordinary meaning, read in the context of the specification and the prosecution history. *Id.* That rule has only two exceptions: when the patentee (1) acts as his own lexicographer and defines a term or phase in the specification, or (2) disavows the full scope of the claim term either in the specification or during prosecution. *Hill-Rom Servs. v. Stryker Corp.*, 755 F.3d 1367, 1373 (Fed. Cir. 2014). Neither exception applies here.

The patent's claim language provides a firm basis for construing a disputed term or phrase. *Phillips*, 415 F.3d at 1314. The patent's disclosure, or specification, is the single best guide to a disputed claim term's meaning. *Id.* at 1315. The prosecution history is also a useful tool in claim construction, as it can reflect the understanding of the patent applicant and the patent examiner as to the intended patent claim scope. *Id.* at 1317. The construction that stays true to the claim language and most naturally aligns with the patent's specification and prosecution history will be, in the end, correct. *Id.* at 1316. Finally, extrinsic evidence shedding light on the understanding of the Ordinary Artisan can also be useful, but such evidence should not be used to contradict the intrinsic evidence. *Id.* at 1318.

III. Technology Tutorial

A. The immune system and the roles of TNF and TNF receptor

A healthy human being's immune system is normally directed toward reacting to and eliminating pathogens, such as a disease-causing virus or bacteria. When a pathogen enters the body, the immune system identifies the pathogen as foreign, surrounds it, and eliminates it. Many molecules regulate the immune system and, when appropriate, trigger an immune response. TNF is involved in the triggering of an immune response. RWD ¶¶ 31-33 & 54.

In healthy humans, TNF and TNF receptors work together to modulate the body's immune response. Low levels of TNF exist naturally in the bloodstream.

Some pathogens, however, cause the body's immune system to increase the amount of TNF in the blood. The increased amount of TNF in the blood stream creates more opportunity for TNF molecules to bind to TNF *receptors* that protrude from certain cells of the immune system. This binding of TNF to the TNF receptor at the cell surface is communicated to the inside of the cell by way of a "signal" through the portion of the TNF receptor that extends through the cell membrane and into the cell. *See id.* ¶¶ 32-33, 41-42 & 45. This "signal" essentially communicates by the presence of TNF at the cell surface that the cell needs to move into action to support an immune response. *Id.* ¶¶ 33, 48 & 54.

The process by which TNF finds the TNF receptor depends on the two molecules coming into close proximity. The shape and characteristics of the TNF receptor are unique to and complement those of TNF—akin to a lock and key. These structures allow the TNF receptor and TNF to "specifically" bind, not just associate with and disassociate with each other in a random manner. Upon binding with TNF, the TNF receptor—which extends inside the cell—signals the cell to initiate a chain reaction of processes through which the pathogen can be neutralized. Those processes will include what a healthy patient will experience as inflammation—but what a diseased patient will experience as tissue damage. RWD ¶¶ 31-33 & 54.

Some people have autoimmune diseases marked by excess free TNF.

Autoimmune diseases, in the most general sense, are diseases in which the immune system mistakenly identifies certain body tissue as foreign and attacks it, much as it would a pathogen. In TNF-related autoimmune diseases, the body produces too much TNF, throwing the immune system, and more specifically the inflammatory response, into overdrive, resulting in injury to healthy tissues. *See id.* ¶ 33 & 53-54.

B. The TNF receptor portion of the patented fusion that is Enbrel

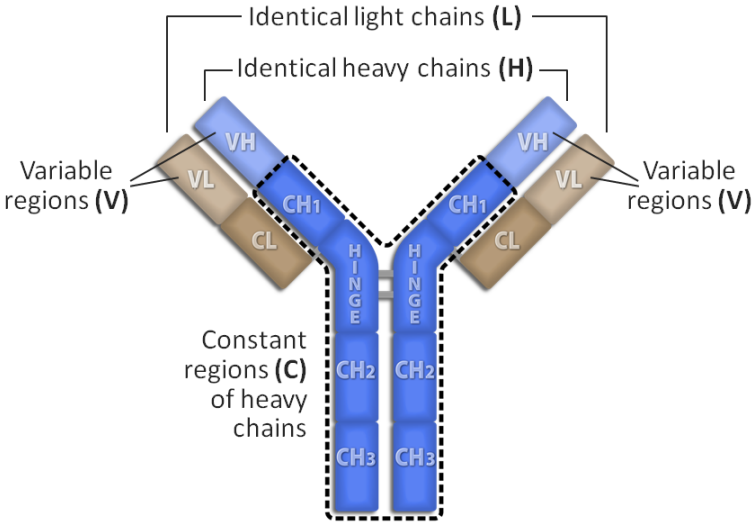
The Roche and Immunex inventions all involve genetically engineered fusion proteins that can be used to mitigate the often-severe inflammatory problems caused by overproduction of TNF in the body. Specifically, the patented inventions concern "fusion" proteins containing two discrete protein fragments. One fragment is a portion of a "TNF receptor," a natural protein configured uniquely to physically bind to TNF at the surface of cells and "signal" inside the cell (essentially communicating by the presence of TNF at the cell surface) that the cell needs to kick into production to support an immune response. *Id.* ¶¶ 69-70. At the time of the Roche Patent filing in 1990, scientists understood that there were two different forms of TNF receptor: "p55" and "p75," so designated because of their molecular weights (55 kilodaltons and 75 kilodaltons, respectively). *Id.* ¶¶ 55-57. The inventions in this case are to fusion proteins that incorporate a TNF receptor fragment from the p75 form ("p75 Receptor Fusions"). *Id.* ¶¶ 82-90.

Proteins have a generalized stickiness; two proteins can loosely bind to

another in a general, non-specific way. But the ability of one protein to bind to another particular target protein and produce a strong and stable bond is what scientists call "specific binding." *Id.* ¶¶ 48-51. The binding of TNF to the TNF receptor is an example of specific binding. Because Enbrel binds specifically to TNF, it prevents TNF circulating in the patient's bloodstream from binding to the natural TNF receptors present on the surface of the immune cells and thereby stops the cell signaling that activates the immune response. *Id.* ¶ 70.

C. **The antibody fragment of the patented fusion protein**

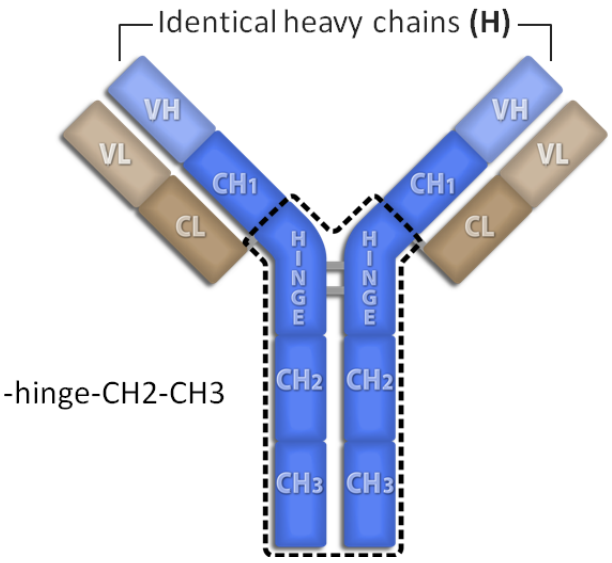
The second fragment of the patented fusion proteins is a portion of an antibody, also called an immunoglobulin. Antibodies are perhaps the most commonly known immune system member, and are produced by B lymphocytes in the blood in response to a specific foreign substance (referred to in these circumstances as an "antigen"). Once produced, antibodies bind the antigen and then recruit white blood cells to destroy the antigen. RWD ¶¶ 7, 58. Antibodies are typically depicted as Y-shaped proteins, as in the figure to the left, with a "variable region" that differs in part from one antibody to another and a "constant



region" that is selected from a limited set of "conserved" or constant sequences. The variable regions are located at the tip of the arms of the "Y" and the constant regions are the remainder of the "Y" structure. Antibodies are composed of four amino acid chains: two identical "heavy chains" and two identical "light chains." The heavy chains are longer in length, and thus "heavier," than the shorter light chains. As shown in the figure, the light chains bind to the portions of the heavy chains that form the arms of the "Y." Importantly, the heavy chains are held together by a "hinge," which structures the antibody into a dimer shape, depicted as the "Y." It can be seen that the two heavy chains each consist of a "variable region" (designated VH) and a "constant region" (designated as CH1, hinge, CH2, and CH3). As shown in the picture, the Y's outside arms each have a light chain variable region (designated VL) and a light chain constant region (designated CL). *See* RWD ¶¶ 60-64.

The antibody variable regions are so named because their amino acid sequences are highly variable from one kind of antibody to another, allowing the creation of a virtually infinite number of antibodies with different variable regions that target different pathogens. The constant regions are so named because their amino acid sequences do not vary between antibodies of the same subclass. *Id.* ¶ 62. The heavy chain constant region's amino acid sequence dictates the antibody's mirror-image dimeric structure and its ability to interact with other immune system

molecules to trigger a pro-inflammatory response. When the antibody binds a pathogen, its constant regions recruit white blood cells to the infection site to attack the pathogen. This "battle" is experienced as inflammation. *Id.* ¶¶ 31 & 33. Although this fragment promotes inflammation, the inventors counter-intuitively used it within their fusion protein aimed at reducing inflammation. *Id.* ¶ 71.



The patent claims describe a fusion protein that must include a specific part of antibody's structure: "all of the domains of the constant region of a human IgG1 heavy chain other than the first domain of the constant region," VWD ¶ 26 & Ex. 24 ('182 Patent 41:28-30). As seen from the figure above, if CH1 is excluded, the remaining domains of the heavy chain constant region are hinge, CH2, and CH3. RWD ¶ 82.

D. The making of the patented fusion protein by bio-engineering cells to include DNA instructions to make this novel protein

Cells in the body make proteins by following the genetic instructions set out in strands of deoxyribonucleic acid ("DNA"). DNA can be thought of as a string of "nucleotide" subunits (abbreviated as "A", "T", "C", or "G"), connected end-to-end in a distinct order or sequence to form a polynucleotide. The nucleotides'

sequence in DNA represents information that a cell can use to make proteins, which are strings of "amino acid" subunits connected end-to-end to form a polypeptide chain (the amino acids are connected by peptide bonds). Each nucleotide triplet, *e.g.*, ATG, codes for one of 20 amino acids. Thus, the DNA sequence provides the instructions for the protein sequence and is said to "code for" that protein. Once made, strings of amino acids do not remain as loose strings. Through natural biological processes, they are processed (amino acids are removed and/or functional features added), re-arranged (for example, in the case of antibodies, into matching pairs), and ultimately folded into unique three-dimensional shapes that confer function (e.g., specific binding or promoting inflammation). RWD ¶ 36-37, 40, & 72-78.

In bio-engineering, DNA coding for a desired protein can be included in a circular DNA molecule called a "vector." Using biotechnology techniques, the vector can then be inserted into a host cell. As with the patented inventions at issue here, the host cell's own protein manufacturing processes can then use the DNA instructions to produce the desired protein. *Id.* ¶¶ 79-81.

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IV. The Roche Patent Claim Terms Have Their Plain Meaning

A. "All of the domains of the constant region of a . . . heavy chain other than the first domain of said constant region" means the "hinge-CH2-CH3" of the heavy chain constant region

"**all of the domains of the constant region of the human IgG[1] immunoglobulin heavy chain other than the first domain of the constant region**"	
Immunex's Construction	**Sandoz's Construction**
"'-hinge-CH2-CH3' region of a human [IgG/IgG1]"	"the CH2 and CH3 domains of human IgG/human IgG1"

The Roche Patent claims use this phrase (and variants of it) to identify those portions of a human antibody heavy chain that are included in (or omitted from) the fusion protein.[1] Sandoz agrees that the Ordinary Artisan understood the constant region of the human antibody heavy chain to be of the structure "CH1-hinge-CH2-CH3" and that the claims expressly require omission of the CH1 domain. *E.g.*, JHD Ex. 2 at 1. By eliminating the first domain, CH1, from this structure as the claims require, plainly what remains of the constant region is exactly Immunex's proposed construction: "hinge-CH2-CH3." But Sandoz asserts that the term "all ***domains***" does not necessarily require retention of the hinge because "domain," in Sandoz's view, had a narrow, specialized meaning that excludes the hinge. Sandoz's position fails in light of (1) the claim language,

[1] With the exception of "IgG" and "IgG1," applied as appropriate for the claims in which they alternatively appear, all variations of this term should have the same construction as proposed by each party. *See* JHD Ex. 1 at 2 n.1 (listing the variations).

(2) the specification, (3) the prosecution history, and (4) extrinsic evidence that has been heavily relied upon in the scientific community for decades. Significantly, the Patent Office's Patent Trial and Appeal Board ("PTAB") construed the claims to require a hinge.

The Roche Patent specification discloses that one of the inventions disclosed in the patent are the recombinant proteins produced by "DNA sequences which combine two partial DNA sequences, one sequence encoding soluble fragments of TNF binding proteins and the other partial sequence encoding all domains except the first domain of the constant region of the heavy chain of human immunoglobulin IgG . . . ." VWD ¶ 26 & Ex. 24 ('182 patent 2:33-39). The description of "all domains except the first," which language is also repeated in the claims, signifies that the first domain is excised and the remainder of the constant region of an antibody is included in the fusion protein.

This description is exemplified in the specification, which teaches that when constructing IgG fusion molecules that consist of "all domains except the first of the constant region of the heavy chain," VWD ¶ 26 & Ex. 24 ('182 Patent 8:56-60), certain IgG vectors (pDC4-Hγ1, and pCD4-Hγ3) are "especially suitable." *Id.* 8:56-9:3. ***Each of those especially suitable vectors codes for a constant region including the hinge***. RWD ¶¶ 101-104. Example 11 uses one of those especially suitable vectors (pCD4-Hγ3) to construct a fusion protein that has "all domains

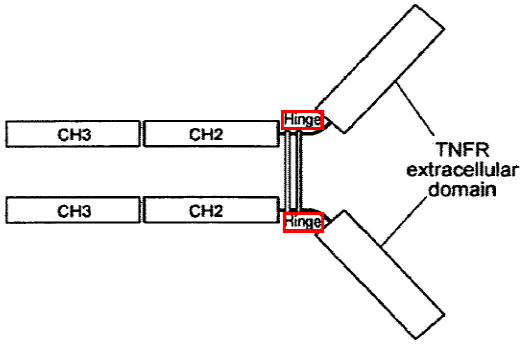
except for the first of the constant region of the heavy chain." VWD ¶ 26 & Ex. 24 ('182 Patent 20:56 – 21:10); RWD ¶¶ 107-109.

The prosecution history aligns with the specification and the claim language. During prosecution, Applicants made clear that the claim language "all domains . . . except the first" includes the hinge: "The immunoglobulin portion of the claimed fusion protein, ***which includes the hinge***, second domain (CH2), and third domain (CH3) of the heavy chain constant region, . . ." VWD ¶ 4 & Ex. 2. Applicants said this—that their claimed inventions included a hinge—not once but repeatedly explained their fusion protein invention as including the hinge-CH2-CH3. *See also* VWD ¶ 5 (collecting exemplary '182 Patent file history citations).[2]

For example, during an appeal, Applicants distinguished prior art (Smith), because their claimed invention retained only hinge-CH2-CH3, whereas the prior art had CH1-hinge-CH2-CH3. VWD ¶ 8 & Ex. 6. Applicants explained their invention to the Examiner as "includ[ing] the hinge, second domain (CH2), and third domain (CH3) of the heavy chain constant region[.]"

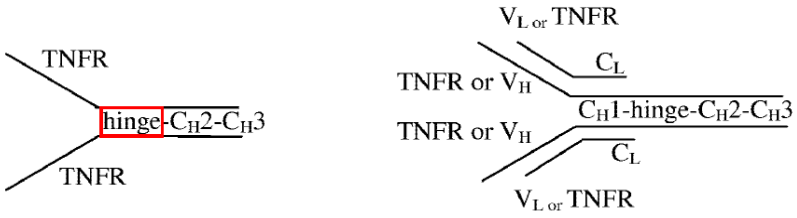
[2] Prior art cited during prosecution is intrinsic evidence for construction purposes. *Phillips*, 415 F.3d at 1317. A patent to Capon, an article by Watson, and a European patent to Seed each describe the hinge as a "domain." RWD ¶ 95. The Patent Office considered each of these references during prosecution, VWD ¶ 6 & Ex. 4, and Sandoz relies on each of these references in its invalidity contentions, *id*. ¶ 7 & Ex. 5.

The claimed invention relates to a fusion protein comprising a soluble fragment of p75 TNFR (*i.e.*, not membrane-bound) and all of the domains of the constant region of a human IgG heavy chain other than the CH1 domain (retaining the hinge, CH2 and CH3 domains). Due to the natural cysteine disulfide bonding that occurs between heavy chains in the hinge region, the resulting fusion protein is homodimeric. The invention is depicted schematically below.



VWD ¶ 9 & Ex. 7 (highlighting and red line and box supplied).

Later, in successfully overcoming a rejection, Applicants' again explained, with clarity, that the claimed fusion protein retained the hinge:



Claimed Molecule

Chimeric antibody molecule of Smith et al.

VWD Decl. ¶ 10 & Ex. 8 (highlighting and red box supplied).

The Applicant's explanation is particularly important because it concerned claim language identical to now-disputed claim language: "all of the domains of the constant region of the human IgG immunoglobulin heavy chain other than the first domain of the constant region." In particular, the Applicants' explanation

concerned claims including then-pending claim 121, which issued as claim 9, and which contains the disputed phrase preceded by a "consists of" transition, VWD ¶ 11 & Ex. 9, which excludes other elements. Thus, the hinge is a required—not optional—aspect of "all of the domains of the constant region of the human IgG immunoglobulin heavy chain other than the first domain of the constant region" in issued '182 Patent claim 9. *See Vehicular Techs. Corp. v. Titan Wheel Int'l, Inc.*, 212 F.3d 1377, 1382-83 (Fed. Cir. 2000). As noted above, claim phrases in different claims mean the same thing.

Significantly, the PTAB has construed the claims as Immunex does. Recently, a third party filed a petition requesting an Inter Partes Review ("IPR") against the '522 Patent, arguing that the claims were invalid over the same art previously cited during the '522 Patent's prosecution and relied upon by Sandoz in this case. In rejecting that IPR petition and the validity attack on the '522 Patent, the PTAB confirmed that the Ordinary Artisan would have understood the claimed phrase "all the domains except the first" to include the "-hinge-CH2-CH3" of a human IgG heavy chain." VWD ¶ 12 & Ex. 10.

Compelling extrinsic evidence also reveals that the Ordinary Artisan would have understood the hinge to be a domain of an immunoglobulin. *Sequences of Proteins of Immunological Interest*, by Dr. Elvin A. Kabat, was the first systematic effort to identify functional boundaries of antibody structure. RWD ¶ 67. Dr.

Kabat's seminal reference described the hinge as a "domain:" "[t]he constant regions of the heavy chains thus ***contain four domains: CH1, hinge, CH2, and CH3***." E. Kabat, *Sequences of Proteins of Immunological Interest* at xix (4th ed. 1987) (emphasis added). VWD ¶ 13 & Ex. 11; RWD ¶ 67 & 96. Similarly, multiple papers on which Sandoz relies in its contentions describe the hinge as a domain: an article by Watson ("terminal to the ***hinge domain***") (JHD Ex. 2 at 22); a European Patent to Seed ("preceding the ***hinge domain***") (*id.* at 22); and a U.S. Patent to Capon ("just upstream of the ***hinge domain***") (*id.* at 22-23).

Finally, even a recent patent application by Sandoz's parent, Novartis, repeatedly identifies the hinge as a "domain:" ¶ 0006 ("a constant region having a CH1 domain, ***hinge domain***, a CH2 domain"); ¶ 0089 ("CH1 domain, ***hinge domain***, a CH2 domain"); and draft claim 8 ("CH1 domain, ***hinge domain***, a CH2 domain"). VWD ¶ 14 & Ex. 12. Novartis's usage, though years after the Roche Patents' filing, is consistent with the understanding at that time—and shows that this understanding still persists. RWD ¶¶ 18, 67 (citing Kabat 1991 edition), 94-98.

Sandoz's position is based on citing certain instances in which the hinge is called a "region" instead of a "domain." But scientists did not (and still do not) use "domain" or "region" with the differential rigidity that Sandoz's position requires. Some references Sandoz proffers did seek to promote nomenclature that might be used to functionally distinguish the hinge from the CH1, CH2, and CH3 by calling

the hinge a "region." But the great weight of scientific evidence, especially the work of Dr. Kabat, shows that the hinge is a significant portion of the constant region of an immunoglobulin and was properly understood as a domain. RWD ¶¶ 16-20, 66-67 & 92-98. Thus, "all the domains except the first domain" includes the hinge-CH2-CH3.

B. "Specifically binds human TNF" means that the patented fusion protein "has the ability to strongly and stably bind human TNF"

"**specifically binds human TNF**"	
Immunex's Construction	**Sandoz's Construction**
"has the ability to strongly and stably bind human TNF"	"binds a detectable amount of TNF in an *in vitro* TNF-binding assay"

The '182 Patent's claims require that both the fusion protein and the insoluble form of the TNF receptor "specifically bind human TNF." Immunex's proposed construction gives meaning to "specifically" as the Ordinary Artisan would have understood it, while Sandoz reads an explicit limitation ("specifically") out of the claims and proposes that the claims should simply read "binds."

The '182 Patent describes the TNF-binding portion of the claimed fusion protein as a soluble fragment of an insoluble human TNF receptor which is then described by three characteristics, the first of which is that it "specifically binds human TNF." The claims also require that the resulting fusion protein "specifically bind human TNF." Importantly, the specific binding ability of the human TNF receptor fragment is not lost in the creation of the fusion protein.

Sandoz agrees that in the human body, TNF is bound by specific receptors on the surface of cells. VWD ¶ 3 & Ex. 1. The human TNF receptor's ability to specifically bind human TNF on the surface of cells comes from the receptor's extracellular region. RWD ¶¶ 23, 42, 57 & 114. Hence the claim requires only that portion of an insoluble human TNF receptor, VWD ¶ 26 & Ex. 24 ('182 Patent, 39:14-15), which is fused to the hinge-CH2-CH3 region of a human antibody, *id.* 39:22-24. Because the resulting fusion protein includes that portion of the natural receptor that *specifically* binds to human TNF, the fusion protein retains the ability to *specifically* bind human TNF, not just exhibit non-specific stickiness. *Id.* 39:25.

As exemplified in the '182 Patent and explained during its prosecution, the Ordinary Artisan would have understood that "specifically binds" is distinguished from "binds" by the character and strength of the binding. Example 1 of the '182 Patent discloses binding assays that distinguish between specific and non-specific binding: "The *specific* ^{125}I-TNF-α binding was determined *after correction for unspecific binding*e The *specific* TNF-binding in the filter test was measured at various TNF concentrations . . . ." VWD ¶ 26 & Ex. 24 ('182 Patent 10:47-51).

During prosecution, the Examiner initially rejected the claims, arguing that that "specifically" was indefinite. Applicants responded:

> Applicants respectfully submit that one of ordinary skill in the art would have clearly understood the meaning of the term 'specifically' after reading the specification. For example, Example 1 (page 21, lines 6-22) notes that

> the desired TNF binding proteins have specific TNF binding activity and discusses an exemplary assay for determining specific TNF binding activity. Thus, the term 'specifically' is not indefinite.

The Examiner thereafter withdrew that indefiniteness rejection. VWD ¶ 15 & Ex. 13 (file history excerpts).

In arguing on appeal against the Examiner's separate rejection of the claims for being obvious over the prior art, Applicants pointed to the high binding affinity for TNF and the kinetic stability of the binding achieved by the claimed fusion proteins. In reversing the Examiner's obviousness rejection, the Board of Patent Appeals found that "The claimed fusion protein additionally had excellent binding activity [and] unexpectedly high kinetic stability." VWD ¶ 17 & Ex. 15.

As Applicants argued, the Ordinary Artisan would understand that "specifically binds" describes binding that is stronger and more stable than non-specific or ordinary binding. RWD ¶¶ 44-45, 111-113 & 115-116. The term is commonly used in the field to convey the concept that one protein has a "preference" for binding to a certain other protein – that is, the two proteins are uniquely configured to preferentially interact with each other. RWD ¶¶ 44-45. That is the qualitative nature of receptors in the body as they preferentially bind to their intended targets. RWD ¶¶ 44-45, 48, & 113. Plaintiffs' construction captures this common-usage understanding in the art. There is no dispute that both Enbrel and Sandoz's copy both specifically bind human TNF.

Sandoz attempts to broaden the claim and delete the specific binding requirement by merely requiring any "detectable" binding. Sandoz's proposed construction of "specific binding"—that it means "binds a detectable amount of TNF in an *in vitro* TNF-binding assay"—conflicts with the specification, the prosecution history, and the understanding of the Ordinary Artisan.

To perform its biological role, TNF receptor does not simply "bind" TNF in any way and to any degree. It binds TNF (1) in a consistent, reproducible way ("stably"), and (2) with strength that is sufficient to allow the purpose of the TNF/TNF receptor binding to be achieved by the follow-on biological processes ("strongly"). RWD ¶¶ 48 & 112-113.

Although the '182 Patent specification distinguishes between specific and non-specific binding, Sandoz ignores this distinction and urges that *any* detectable amount of binding is sufficient. This makes no distinction between reproducible, high-affinity binding and the random stickiness that proteins generally have. RWD ¶¶ 44-52 & 111-117. Random, non-specific binding is the very binding that the claims, specification, and art on which Sandoz otherwise relies (*e.g.*, *Smith*) expressly ***distinguish*** from specific binding.

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C. "Wherein the polynucleotide encodes a protein consisting of" means "the polynucleotide contains the genetic information for a protein consisting of"

"wherein the polynucleotide encodes a protein consisting of"	
Immunex's Construction	**Sandoz's Construction**
"wherein the polynucleotide contains the genetic information for a protein consisting of"	"the polynucleotide encodes only the protein and includes no other amino acid sequence"

As explained above in § I(A)(2), by 1990 scientists were able to program cells, called "host cells," to produce proteins that the cell did not otherwise make, including man-made proteins. This was done by introducing DNA into the cell that included, among other things, the genetic information for the desired protein. "Encodes" describes the coded relationship between the sequence of nucleotides in the DNA and the sequence of amino acids in the protein. Thus, the DNA codes for, or encodes, the protein sequence. The host cell then uses the inserted DNA to make the desired protein along with the other proteins and peptides normally made by the cell. This was basic, common knowledge to a scientist in 1990.

Sandoz does not dispute this, and in fact does not offer a definition of "encodes" but includes "encodes" in its proposed construction. Rather, the dispute that Sandoz brings regards the meaning of the words "consisting of" in relation to the genetic content of the polynucleotide. Sandoz attempts to read in a limitation that the polynucleotide encodes "only" the protein sequence and cannot encode any additional amino acids. There are two separately fatal defects with Sandoz's

position. One regards the law; the other regards the science, as the specification plainly sets out.

The full relevant text of the applicable method claims (1 and 7 of the '522 Patent) is, with emphasis supplied: "A method ***comprising*** the steps of: (a) culturing a host cell ***comprising*** a polynucleotide, wherein the polynucleotide encodes a protein ***consisting of*** . . . ." VWD ¶ 19 & Ex. 17 ('522 Patent 45:45-49). It is long-settled law that "comprising" is an open-ended transitional phrase—*i.e.*, when "comprising" is used in the preamble it signifies that the invention must have the specified limitations, but is not prevented from encompassing more. *E.g.*, *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003).

It is correct that when a claim uses the closed "consisting of" transitional phrase in the preamble, it can signal that the invention must include only the identified limitations and, thus, precludes non-listed features or steps. But that principle is not relevant here, because both claims 1 and 7 use "comprising" in two places ahead of "consisting of" in the claims. In those circumstances, "consisting of" limits only the elements set forth in the particular clause following it and does not preclude additional elements. *E.g.*, *Mannesmann Demag Corp. v. Engineered Metal Prods. Co.*, 793 F.2d 1279, 1282 (Fed. Cir. 1986).

Despite its absence from the language leading up to the transitional phrase, Sandoz gratuitously adds the word "only" after "encodes." But nothing in the

specification or file history justifies the creation of that new limitation. Indeed, the argument Sandoz makes here is like the argument the Federal Circuit rejected in *In re Crish*, 393 F.3d 1253 (Fed. Cir. 2004), which involved a claim to: "A purified oligonucleotide ***comprising*** at least a portion of the nucleotide sequence of SEQ ID NO: 1, wherein said portion ***consists of*** the nucleotide sequence from 521 to 2473 of SEQ ID NO: 1, and . . . ." *Id.* at 1254 (emphasis supplied). The Federal Circuit rejected the very same type of argument Sandoz advances here, explaining that as a matter of patent claim construction law, "the term 'consists' limits the 'said portion' language to the subsequently recited number nucleotides, ***but the earlier term 'comprising' means that the claim can include that portion plus other nucleotides***." *Id.* at 1257 (emphasis supplied). *Crish* resolves Sandoz's argument as step (a) in the '522 Patent method claims recites "culturing a host cell ***comprising*** a polynucleotide" which allows the presence of other nucleotides in addition to those that encode the TNF receptor protein fragment. These additional nucleotides can code for additional amino acids.

The '522 Patent specification fully supports this construction, as it discloses that additional nucleotides are included in the host cell and or vectors (including nucleotides encoding other proteins and peptides), some of which are involved in producing the desired protein. To make a desired protein, a host cell, for example, must have cellular machinery and be given proper instructions. The cellular

machinery is itself made according to other instructions encoded in the host cell's polynucleotides. And the instructions for the desired protein are not necessarily limited to those nucleotides coding for the amino acids of the final protein product. In addition to instructions dictating the sequence of the desired protein, there can be instructions for other proteins and peptides that can be produced alongside the desired protein to aid, for example, in its secretion into the extracellular space. *E.g.*, VWD ¶ 19 & Ex. 17 ('522 Patent 18:46 (the "cDNA coding for the extracellular part" also contained genetic instructions for a signal peptide needed to aid in the secretion of the desired protein)); RWD ¶¶ 73-78. Under such circumstances, after a string of amino acids (a "polypeptide chain") is made, the cell performs further processing to yield the desired protein. RWD ¶ 78. The specification and the art certainly contemplated this. Immunex's construction aligns both with the claims and the science in the specification. RWD ¶¶ 118-122. Sandoz's position aligns with neither and should be rejected.

V. The Immunex Patent Claim Terms Have Their Ordinary Meaning

The claims of the '225, '605, and '631 Patents recite methods of using Enbrel to treat psoriasis and psoriatic arthritis. Psoriasis is a human disease that manifests primarily via skin symptoms. Psoriatic arthritis is a related condition which involves both psoriasis skin symptoms and arthritis symptoms. As of the filing date of the Immunex Patents in 1999, physicians readily diagnosed each of

these diseases.

Ignoring the intrinsic record, Sandoz contends that the terms "psoriasis," "psoriatic arthritis," and "ordinary psoriasis" are indefinite and not capable of a construction. Alternatively, Sandoz disputes the plain and ordinary meaning of these three terms and one other disease term, "plaque psoriasis." Sandoz also contests the meaning of the term "patient." But the patent specification, the prosecution history, and the understanding of the Ordinary Artisan make clear that these claim terms should be given their plain and ordinary meanings.

A. "Psoriasis" is a particular human inflammatory skin disease, as diagnosed by physicians

"**Psoriasis**"	
Immunex's Construction	**Sandoz's Construction**
"a particular human inflammatory disease of the skin and/or nails, as diagnosed by physicians"	indefinite under 35 USC § 112 or, alternatively, "an inflammatory disease of the skin and/or nails that does not include symptoms of psoriatic arthritis"

As the '225 Patent explains, psoriasis is an "inflammatory skin disease . . . characterized by epidermal keratinocyte hyperproliferation," GD Ex. 1 ('225 Patent 1:51-54), *i.e.*, the excessive build-up of cells on the surface of the skin.[3] The extra skin cells form fine, silvery scales and itchy, dry red patches. GD ¶ 28. Physicians have diagnosed it since the early 1800s. *Id.* ¶ 27. The Ordinary Artisan, a dermatologist, in 1999 would have readily been able to diagnose psoriasis. *Id.*

[3] The '225, '605, and '631 Patents share a common specification. For brevity, this brief uses representative citations to the '225 Patent's column and line numbers.

¶ 28. This is confirmed by the "background" discussion in the '225 Patent that references several articles and a rheumatology textbook describing the etiology of psoriasis and psoriatic arthritis. *See* GD Ex. 1 ('225 Patent 1:49-61). The '225 Patent further describes psoriasis and psoriatic arthritis as "different clinical entities," *id.* at 1:58-59, suggesting that physicians diagnose the diseases by examining the patients. Thus, Immunex proposes a simple construction that relies on the description in the '225 Patent and includes the reality that such a disease would be diagnosed by a physician. GD ¶ 30-31.

In contrast, Sandoz initially asserts that the Ordinary Artisan would not have understood what "psoriasis" meant in 1999, and therefore, the claim term is indefinite. The Supreme Court recently instructed that a claim term cannot be indefinite unless, read in light of the specification and the prosecution history, it fails to inform, with reasonable certainty, those skilled in the art about the invention's scope. *Nautilus, Inc. v. Biosig Instruments*, 134 S. Ct. 2120, 2124 (2014). But the '225 Patent does describe "psoriasis," and even without that, the ordinary meaning of "psoriasis" was so well known to an Ordinary Artisan in 1999, a dermatologist, that it would defy logic to suggest she wouldn't have known the scope of the disease intended to be treated by the claimed methods. GD ¶ 26-28, 30.

Moreover, the claims of the '225 Patent require "at least fifty percent

improvement in PASI score" ("**p**soriasis **a**rea and **s**everity **i**ndex"), GD Ex. 1 ('225 Patent 15:39-49), a skin test physicians use to measure changes in the surface area and the degree of inflammation affected by psoriasis. GD ¶ 29. Sandoz doesn't challenge the meaning of that claim phrase.[4] So the '225 Patent describes psoriasis and a way to measure the improvement of psoriasis as a result of treatment with Enbrel.

Further, Sandoz's proposed Ordinary Artisan is "an ***M.D. with*** a specialization in rheumatology or dermatology, and ***experienced in the*** study and/or ***clinical treatment of psoriasis*** and/or psoriatic arthritis." VWD ¶ 22 & Ex. 20 (emphasis supplied). Presumably, if doctors treated psoriasis, then they understood what it was. Under *Nautilis*, the specification and Sandoz's own proposed definition of an Ordinary Artisan rebut the notion that an Ordinary Artisan would not have understood what "psoriasis" meant.

Turning next to Sandoz's alternative construction of "psoriasis," it fails on a couple points. First, Sandoz omitted "human" from its proposal. Immunex included "human" because psoriasis was a known human disease and there was no credible evidence that suggested it could exist in any non-human animal. GD ¶ 36 (citing Schön); *see also id.* ¶¶ 37-39.

[4] *See* VWD ¶ 21 & Ex. 19 (reporting that 70.5% of patients on Sandoz's biosimilar (GP2015) achieved a "PASI 75" improvement by week 12).

Second, it is wrong for Sandoz to have carved out from its definition of "psoriasis" any condition that also includes symptoms of psoriatic arthritis. This has the effect of rendering logically impossible any concept of a patient having both psoriasis and psoriatic arthritis. GD ¶¶ 33, 35. Such construction is contradicted by the claims,[5] the specification,[6] and the prosecution history[7] of the patents—all of which indicate that a patient can have ***both*** psoriasis and psoriatic arthritis. *Id.* ¶ 34.

B. "Psoriatic arthritis" is a particular human inflammatory disease of the skin and joints, as diagnosed by physicians

"**Psoriatic arthritis**"	
Immunex's Construction	**Sandoz's Construction**
"a particular human inflammatory disease, as diagnosed by physicians, characterized by one or more swollen joints or one or more painful or tender joints, and also manifest at least one psoriatic lesion of the skin or nails before or after the onset of joint symptoms"	Indefinite under 35 USC § 112 or, alternatively, "an inflammatory disease characterized by one or more swollen joints or one or more painful or tender joints, and also manifest at least one psoriatic lesion of the skin or nails prior to or concurrent with the onset of joint symptoms"

The '225 Patent describes psoriatic arthritis as "a chronic autoimmune

[5] Claim 12 of the '225 Patent covers a method of treating "a patient having psoriasis *and* psoriatic arthritis." GD Ex. 1 (emphasis supplied). Similarly, claim 1 of the '631 Patent recites a method of treating "a patient having psoriatic arthritis and/or plaque psoriasis." GD Ex. 3.

[6] "[A] minority of psoriasis sufferers actually have PsA." GD Ex. 1 ('225 Patent 1:65-2:3); *see also* GD ¶ 34.

[7] During the '605 Patent's prosecution, the Examiner stated that "about ten percent of people with psoriasis develop psoriatic arthritis." VWD ¶ 24 & Ex. 22 ('605 file history, Office Action dated June 3, 2011 at 2-3).

condition that shares some features with both rheumatoid arthritis (RA) and the inflammatory skin disease psoriasis." GD Ex. 1 ('225 Patent 1:49-51). RA involves pain and swelling in the joints. The '225 Patent gives further definition to psoriatic arthritis by stating: "patients are defined as having psoriatic arthritis (PsA) if they have one or more swollen joints or one or more painful or tender joints, and also manifest at least one psoriatic lesion of the skin or nails." *Id.* at 12:34-37. Again, the '225 Patent provides literature references that discuss the etiology of psoriatic arthritis, and the patent describes it as a different clinical entity from psoriasis. *Id.* at 1:49-64. Like psoriasis, psoriatic arthritis was well-known before 1999, the filing date of the '225 Patent, GD ¶ 43 (citing Bruce & Gladman), and thus would have been easily understood by the Ordinary Artisan at the time of the invention. GD ¶ 43-44.

Sandoz's disputes regarding "psoriatic arthritis" largely mirror those regarding "psoriasis." Sandoz's first alternative position—that the Ordinary Artisan would not have understood the term "psoriatic arthritis"—is, again, belied by the description in the specification and the knowledge of the disease by an Ordinary Artisan, GD ¶ 42-45, who according to Sandoz's definition is an M.D. who treats that disease. As above, if doctors could treat psoriatic arthritis, presumably they understood what it was. And, as with psoriasis, the specification discusses psoriatic arthritis: what it is, GD Ex. 1 ('225 Patent 1:49-58; 12:34-37);

some of its symptoms that physicians would diagnose, *id.* at 1:65-2:3; 12:34-37; its overall prognosis, *id.* at 1:61-64; and ways to measure it, *id.* at 17:62-65. In light these facts, an Ordinary Artisan would have understood what "psoriatic arthritis" meant and there is no basis for arguing that the term is indefinite. GD ¶¶ 42-45.

While Sandoz effectively agrees that the Ordinary Artisan would have understood this claim phrase to be an inflammatory disease of the skin and joints, Sandoz omits from its proposal three other necessary features of the disease: that the onset of joint symptoms can occur before or after skin symptoms, that psoriatic arthritis is a human disease, and that physicians diagnose it.

First, Sandoz excludes instances in which joint symptoms precede skin symptoms. But the specification teaches that, in psoriatic arthritis, "[t]he psoriatic lesions may appear ***before or after*** the onset of swollen or tender joints." GD Ex. 1 ('225 Patent 12:34-39) (emphasis supplied); *see also* GD ¶ 47. Sandoz is clearly cherry-picking portions of the specification that suit its goals: Sandoz is using one sentence from the specification in its construction,[8] but proposing the opposite of the immediately following sentence.[9]

[8] "For purposes of this invention, patients are defined as having psoriatic arthrisis [sic] (PsA) if they have one or more swollen joints or one or more painful or tender joints, and also manifest at least one psoriatic lesion of the skin or nails." GD Ex. 1 ('225 Patent 12:34-37).

[9] "The psoriatic lesions may appear ***before or after*** the onset of swollen or tender joints." GD Ex. 1 ('225 Patent 12:37-39) (emphasis supplied).

Second, Sandoz contends that psoriatic arthritis is not limited to humans. But Sandoz cited no studies showing that animals get psoriatic arthritis, and Immunex's independent expert is aware of none. GD ¶ 48. In addition, the '225 Patent's specification explains that one primary endpoint for determining improvement or worsening of psoriatic arthritis is the "Psoriatic Arthritis Response score." GD Ex. 1 ('225 Patent 17:9-13). This measure includes several components, one of which is a "patient self-assessment," *id.*, which necessarily must involve a human.

Third, Sandoz ignores that physicians diagnose psoriatic arthritis. But it takes an examination by a physician to diagnose the disease. GD ¶ 44; *see also* GD Ex. 1 ('225 Patent 17:9-13).

C. "Ordinary psoriasis" is psoriasis without the more serious symptoms of psoriatic arthritis

"**Ordinary Psoriasis**"	
Immunex's Construction	**Sandoz's Construction**
"psoriasis without the more serious symptoms of psoriatic arthritis"	"an inflammatory disease of the skin and/or nails that does not include the symptoms of psoriatic arthritis" or indefinite under 35 USC. § 112

The '605 Patent claims "[a] method for treating a patient having ordinary psoriasis," and its specification discusses features of "ordinary psoriasis." Indeed, the specification's detailed delineation of "ordinary psoriasis," *see* GD Ex. 2 ('605 Patent 14:21-35), is wholly sufficient to confirm the meaning of the term. As the

specification describes, "[p]atients are defined as having ordinary psoriasis if they lack the more serious symptoms of PsA [listing such symptoms] . . . but have one of the following" seven subtypes of psoriasis. *Id.* The specification further explains that patients have "ordinary" psoriasis if they lack the more serious symptoms of" psoriatic arthritis," *id.* at 14:14-17.

Sandoz alternatively argues that the Ordinary Artisan would not have understood this term. That argument fails for the same reasons that its similar indefiniteness arguments fail regarding psoriasis and PsA. The term "ordinary psoriasis" is not indefinite, because the patent describes in detail what types of patients would be subject to such diagnosis. *Id.* at 14:21-35; *see also* GD ¶ 52. In addition, the Ordinary Artisan's knowledge from the literature and clinical practice informs those skilled in the art about the invention's scope. *Nautilus*, 134 S. Ct. at 2124.

Sandoz's position flouts plain meaning. First, it conflates "psoriasis" and "ordinary psoriasis." But the Immunex Patents plainly distinguish the two and the Patent Office agreed by issuing a patent for the treatment of each disease. The '605 Patent recites in claim 1 a method for treating a patient having ordinary psoriasis. The '225 Patent recites in claim 1 a method for treating a patient having psoriasis. Just as a "baffle" was different from a "steel baffle" in *Phillips*, so "psoriasis" and "ordinary psoriasis" are different in the Immunex Patents.

Second, Sandoz's position ignores the specification. Sandoz asserts that the symptoms of "ordinary psoriasis" can never include the symptoms of psoriatic arthritis. But the specification—usually the best (and often dispositive) guide to construction—explains that "ordinary psoriasis" may have some joint pain "but does not involve the extreme pain and often deforming degeneration of joints and bone that occurs in PsA patients." GD Ex. 2 ('605 Patent 2:3-6). The specification further explains that patients have "ordinary psoriasis if they ***lack the more serious symptoms*** of" psoriatic arthritis, *Id.* at 14:14-17 (emphasis supplied). The emphasized text necessarily means that a patient having ordinary psoriasis may also have some symptoms of psoriatic arthritis—just not the more serious ones. GD ¶¶ 52, 54. That is exactly Immunex's construction.

In addition to contradicting the specification, Sandoz's position is illogical. Excluding all psoriatic arthritis symptoms—as Sandoz seeks to do—will necessarily exclude all psoriasis symptoms. GD ¶ 55. But according to Sandoz's own proposed construction, "psoriatic arthritis" includes symptoms of psoriasis. Sandoz's proposed constructions of "ordinary psoriasis" and "psoriatic arthritis" therefore result in the paradoxical situation where "ordinary psoriasis" excludes the symptoms of psoriasis. *Id.*

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D. **"Plaque psoriasis" is a subtype of psoriasis**

"**Plaque Psoriasis**"	
Immunex's Construction	**Sandoz's Position**
"a subtype of psoriasis, characterized by inflamed swollen skin lesions covered with silvery white scale"	"an inflammatory disease of the skin characterized by inflamed swollen skin lesions covered with silvery white scale"

Tellingly, Sandoz does not argue that plaque psoriasis is indefinite. The only disputes that remains concerning the parties' proposed constructions of "plaque psoriasis" is whether plaque psoriasis was understood to be a subtype of psoriasis. The '631 Patent includes claims to methods of treating patients with "plaque psoriasis," a subtype of psoriasis in which the skin lesions have silvery white scale. GD Ex. 3 (independent claims 1& 8); GD ¶ 58, 60. The '631 Patent specification describes "plaque psoriasis" in its listing of psoriasis subtypes in the definition of "ordinary psoriasis" at Col. 14:24-26: "inflamed swollen skin lesions covered with silvery white scale (plaque psoriasis or psoriasis vulgaris)." GD Ex. 3. This description comports with the plain and ordinary meaning of "plaque psoriasis," GD ¶¶ 59-61 & Ex. 16. Immunex's construction reflects this description.

Sandoz does not dispute Immunex's explanation. In particular, Sandoz does not dispute that plaque psoriasis is an inflammatory disease of the skin, that it is characterized by skin lesions, or that those lesions have silvery white scale. The parties' sticking point is that Sandoz does not agree to the obviously plain point that plaque psoriasis is a subtype of psoriasis, and it is unclear to Immunex why

that is so. Sandoz's proposed construction ignores the context in which Sandoz's proposed language appears. The plain and ordinary meaning of "plaque psoriasis" to an Ordinary Artisan in August of 1999 was that plaque psoriasis is a subtype of psoriasis. GD ¶¶ 60-61, 63 & Ex. 17. Also, the specification uses "plaque psoriasis" in a way that is consistent with the plain and ordinary meaning, for example, when it lists a number of subtypes of psoriasis (such as "plaque psoriasis," "guttate psoriasis," and "inverse psoriasis") with characteristics that distinguish one subtype from another; in such a context, there was no need to reiterate that each is a subtype of psoriasis. GD ¶ 61.

E. **"Patient" here means a human (not animal) in need of treatment**

"**Patient**"	
Immunex's Construction	**Sandoz's Proposal**
"human in need of treatment"	"any animal, including a non-human animal"

The claims of the '225, '605, and '631 Patents describe treatment of patients with human inflammatory disease—psoriasis, ordinary psoriasis, plaque psoriasis, and psoriatic arthritis. The patents' specification and the prosecution history are consistent with the common understanding that a "patient" is a human being. For example, the patents' specification states that "Ordinary psoriasis may be treated by administering to a ***human*** patient compositions containing a therapeutically effective amount of a TNFα inhibitor such as a soluble TNF receptor or an antibody against TNFα." GD Ex. 1 ('225 Patent 14:29-32) (emphasis supplied). "In

one exemplary regimen for treating adult ***human*** patients, 25 mg of TNFR:Fc is administered by subcutaneous injection two times per week . . . ." *Id.* at 14:40-42. This dose of 25 mg two times per week is the same dose recited in some of the claims of the '225 Patent. "Sixty patients with active psoriatic arthritis (PsA) were enrolled in a Phase II double-blind randomized, placebo controlled study to determine whether the subcutaneous biweekly administration of [Enbrel] was safe in this patient population and whether efficacy could be documented for both the arthritic and psoriatic aspects of this disease." *Id.* at 16:18-24. Of course, these were human patients. And not everyone is a patient—being a patient indicates a need for medical treatment. GD ¶ 70.

While the patents' common specification mentions that "[i]n addition to human patients, inhibitors of TNFα are useful in the treatment of autoimmune and inflammatory conditions in non-human animals," GD Ex. 1 ('225 Patent at 15:61-63), in the context of the patent claims, "patients" are properly limited to humans because the diseases to be treated by the claimed methods are only human diseases: psoriasis, ordinary psoriasis, psoriatic arthritis, and plaque psoriasis. GD ¶¶ 36-39, 48, 67. Similarly, the other elements of the claims – PASI score improvement and the dosing schedule of 25 mg twice a week – are clearly only applicable to human patients. *Id.* ¶ 69. Because Enbrel is a fusion protein made of parts of different human proteins, the Ordinary Artisan would not have used Enbrel to treat disease

in a non-human for fear of causing a reaction. *Id.* ¶ 68.

As *Phillips* instructs, claim terms other than the disputed term can help guide the proper construction of the disputed term. *Phillips*, 415 F.3d at 1314 (approving precedent that construes "ingredients" in light of "mixture" in the same claim). That is true here. Some claims require an improvement in the "PASI score." *E.g.*, GD Ex. 1 ('225 Patent, claim 1). PASI is not used to assess non-human animals, GD ¶ 69, (and non-humans don't suffer from these human diseases anyway, *id.* ¶¶ 36, 38, 67). Thus the claims point away from Sandoz's proposed construction.[10]

VI. Conclusion

Phillips teaches "'[t]he construction that stays true to the claim language and most naturally aligns with the patent's description of the invention will be, in the end, the correct construction.'" *Phillips*, 415 F. 3d at 1316. Immunex's proposals most naturally align with each of these—and with the prosecution history, intrinsic art (including art that Sandoz otherwise relies on), other credible, contemporaneous intrinsic evidence, and, in some cases, patents filed by Sandoz's corporate parent.

[10] The Immunex Patents' text settles that a "patient" is "a human in need of treatment." Dictionary definitions also support Immunex's construction. *See* JHD Ex. 3 at 77-78 at Ex. B; GD ¶ 71. Sandoz did not cite dictionaries in the JCCS, and thus cannot rely on any now. In any event, that Sandoz has found broader dictionary definitions merely shows that the meaning of "patient" is context-dependent. In the Immunex Patents' context—treating a human disease with a therapeutic derived from human proteins—it does not make sense for a patient to be anything other than a person. GD ¶¶ 67-68; *see also* '225 Patent at 16:6-11.

Sandoz's proposals, however, do not align with the claim language, specification, or prosecution history. They only loosely align with inconsistent, cherry-picked extrinsic evidence—which, under *Phillips*, is entitled to no weight.

Immunex respectfully requests that the Court adopt its constructions.

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Respectfully submitted,

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